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ORIGINAL RESEARCH

Prediction of Spirometric Indices Using Forced Oscillometric Indices in Patients with Asthma, COPD, and Interstitial Lung Disease

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Background and Objective: Spirometry is sometimes difficult to perform in elderly patients and patients with cognitive impairment. Forced oscillometry (FOT) is a simple, noninvasive technique used for measuring respiratory impedance. The aim of this study was to develop regression equations to estimate vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume in 1 s ($FEV_{1.0}$) on the basis of FOT indices and to evaluate the accuracy of these equations in patients with asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD).

Materials and Methods: We retrospectively included data on 683 consecutive patients with asthma (388), COPD (128), or ILD (167) in this study. We generated regression equations for VC, FVC, and $FEV_{1.0}$ by multivariate linear regression analysis and used them to estimate the corresponding values. We determined whether the estimated data reflected spirometric indices.

Results: Actual and estimated VC, FVC, and $FEV_{1.0}$ values showed significant correlations (all r > 0.8 and $P < 0.001$) in all groups. Biases between the actual data and estimated data for VC, FVC, and $FEV_{1.0}$ in the asthma group were −0.073 L, −0.069 L, and 0.017 L, respectively. The corresponding values were −0.064 L, 0.027 L, and 0.069 L, respectively, in the COPD group and −0.040 L, −0.071 L, and −0.002 L, respectively, in the ILD group. The estimated data in the present study did not completely correspond to the actual data. In addition, sensitivity for an $FEV_{1.0}$/FVC ratio of <0.7 and the diagnostic accuracy for the classification of COPD grade using estimated data were low.

Conclusion: These results suggest that our method is not highly accurate. Further studies are needed to generate more accurate regression equations for estimating spirometric indices based on FOT measurements.

Keywords: forced expiratory volume in 1 second, forced oscillation technique, forced vital capacity, spirometry, vital capacity

Plain Language Summary

Spirometry is the most commonly used pulmonary function test. However, the forceful expiratory and inspiratory maneuvers in spirometry require good patient cooperation. Elderly patients and patients with cognitive impairment sometimes face difficulties in undergoing spirometry. The forced oscillometry (FOT) is a simple, noninvasive technique used for measuring the resistance and reactance of the respiratory system. However, it is difficult to interpret the data obtained, because reference values of FOT data at a global level have not been established yet. We aimed to determine whether forced oscillometry (FOT) data reflect spirometric indices in patients with asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease. We generated regression equations for vital capacity (VC),

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forced vital capacity (FVC), and forced expiratory volume in 1 s ($FEV_{1.0}$) on the basis of FOT indices and used them to estimate the corresponding values. We determined whether the estimated data reflected spirometric indices. Actual and estimated spirometric indices showed significant correlations, and the root mean squared errors in the present study were smaller than those in our previous study. However, the estimated data in the present study did not completely correspond to the actual data. In addition, sensitivity for an $FEV_{1.0}$/FVC ratio of <0.7 and diagnostic accuracy for COPD grade using estimated data were low. Further studies are needed to generate more accurate regression equations for estimating spirometric indices based on FOT measurements.

Introduction

Spirometry is widely used to assess indices of lung function, including vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume in 1 s ($FEV_{1.0}$), to diagnose respiratory diseases and to quantify the severity of respiratory impairment. However, its use may be sometimes difficult in elderly patients, patients with cognitive impairment, and those with severe respiratory distress, because maximum effort is required during forced expiratory maneuvers.[1] Therefore, alternative methods for measuring lung function are needed for these populations.

The forced oscillometry (FOT) is a simple, noninvasive technique used for measuring the resistance and reactance of the respiratory system.[2] It can be performed easily in pediatric patients[3,4] and in adults who are unable to undergo spirometry.[2,5] However, it is difficult to interpret the data obtained, because reference values of FOT data at a global level have not been established yet. Although several studies have reported the reference values of FOT data,[6] it was also reported that the normal values of resistance (Rrs) and reactance (Xrs) differ depending on ethnicity, sex, standing height, age, body weight, oscillometric devices, and measuring techniques.[7] In Japan, reference values for FOT measurements in middle-aged and elderly Japanese individuals have been published.[8] However, 44.8% of the population included in that study had abnormal spirometric findings, and it is unclear how many subjects had abnormal chest radiography findings. Therefore, the reliability of these reference values is debatable.

To solve this problem, we previously generated regression equations to estimate VC, FVC, and $FEV_{1.0}$ on the basis of FOT indices reported in our previous study.[9] We demonstrated that estimated VC, FVC, and $FEV_{1.0}$ correlated significantly with the actual data in both development and validation studies. However, the estimated data in the validation study did not show high accuracy. We hypothesized that this was a result of including heterogeneous subjects (healthy populations and patients with various respiratory diseases).

To verify the above hypothesis, we separately generated regression equations for VC, FVC and $FEV_{1.0}$ in patients with asthma, chronic obstructive pulmonary disease (COPD), or interstitial lung disease (ILD) and estimated the corresponding values. Furthermore, we determined whether the estimated data reflected spirometric indices in each patient group.

Materials and Methods
Study Population

This retrospective study included data on consecutive patients who simultaneously underwent FOT and spirometry at Ehime University Hospital (n = 2294) between January 1, 2010 and December 31, 2017 and at Sumitomo Besshi Hospital (n = 1287) between April 1, 2013 and March 31, 2016 (In addition to patients included in the previous study,[9] we included patients of Ehime University Hospital [January 1, 2016 to December 31, 2017] in this study). FOT was performed routinely in patients who visited the respiratory division of each of the participating institutions.

Subjects who were diagnosed with asthma, COPD, or ILD were included in this study. Subjects were excluded if they were unable to undergo spirometry simultaneously with FOT, were aged <17 years, were not Japanese, did not have asthma, COPD or ILD, or had overlapping respiratory diseases. Subjects whose spirometric performance did not meet the spirometry criteria of the American Thoracic Society (ATS)/European Respiratory Society (ERS)[10] were also excluded.

Forced Oscillometry

Respiratory impedance was measured using a commercially available multifrequency impulse FOT device (MostGraph-01; Chest MI, Tokyo, Japan) as reported previously.[11–13] The measurements were made in accordance with recent guidelines.[6] Impulse oscillometry signals generated by a loudspeaker at intervals of 0.25 s were applied to the respiratory system through the mouthpiece during tidal breathing at rest. The mouth pressure and flow signals were recorded, which were used to calculate Rrs and Xrs against oscillatory frequency ranging from 4 Hz to 36 Hz.

Coherence values of <0.9 and variability coefficients of Rrs of >10% were excluded. During measurements, patients were breathing in a relaxed and stable manner and seated in an upright posture with correct head position, cheek support, mouthpiece seal, and tongue position. Each patient took at least 60 s for the examination. The artefacts such as leaks, cough, glottis closure, or unusually large breaths were excluded. The acquisition was repeated until a minimum of three tidal breaths that met these requirements were obtained. Oscillatory index was expressed as the mean value during a respiratory (whole-breath) cycle, inspiratory and expiratory phases. The oscillatory index in the whole-breath phase was used. FOT was performed prior to spirometry.

Spirometry

Spirometry was performed according to the method described in the ATS/ERS guidelines.[10] Pulmonary function indices, including VC, FVC, and $FEV_{1.0}$, were measured by spirometry. Predicted normal values for VC, FVC, and $FEV_{1.0}$ were calculated using the equation devised by the Japanese Respiratory Society, as reported previously.[14] Pulmonary function indices were calculated as percentages of predicted normal values (described as %VC, %FVC and %$FEV_{1.0}$).

Definitions

Diagnosis of asthma was based on the clinical history of characteristic symptom patterns (wheeze, shortness of breath, chest tightness, and cough that vary over time) and evidence of reversible airway obstruction. COPD was diagnosed using a post-bronchodilator ratio ($FEV_{1.0}$/FVC) of <0.7 according to the Global Initiative for Obstructive Lung Disease criteria.[15] In addition, a smoking history of more than 10 pack-years or long-term biomass exposure were included as eligibility criteria for COPD in this study. ILD was diagnosed in accordance with the clinical criteria established by the current ATS/ERS guidelines.[16] Multidisciplinary diagnosis was made using clinical data such as presentation, exposures, smoking status, associated diseases, lung function, laboratory findings, and radiologic findings.

Calculation of Estimated VC, FVC, and $FEV_{1.0}$

Previously, we identified parameters predictive of VC, FVC, and $FEV_{1.0}$ using anthropometric variables (age, sex, height, and body weight) and FOT indices.[9] According to the previously described method, we newly generated separate regression equations for VC, FVC and $FEV_{1.0}$ for patients
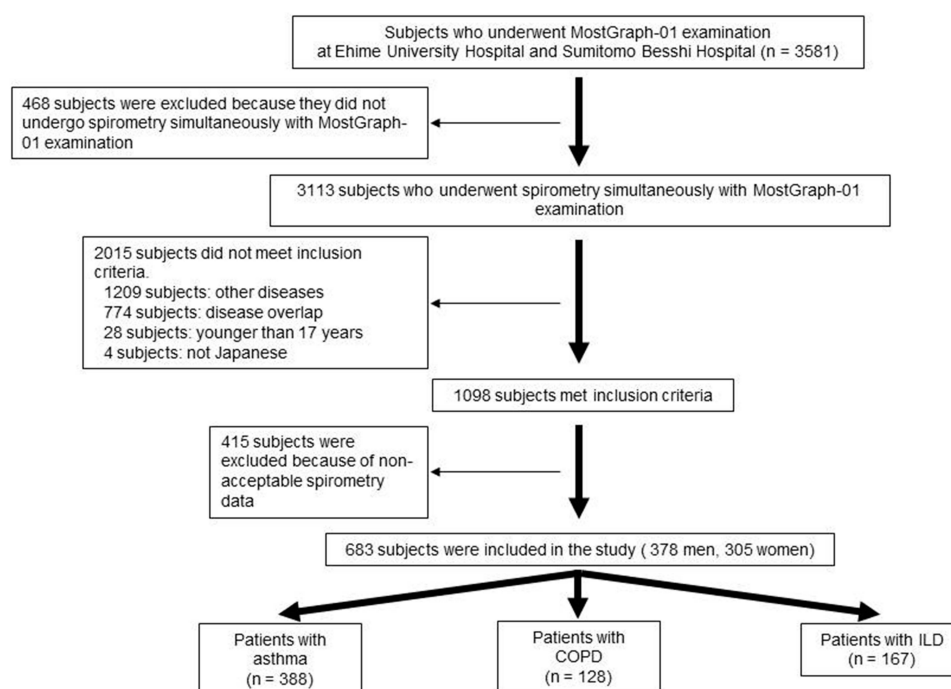
Figure 1 Flow chart showing recruitment of study participants.
Abbreviations: COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

with asthma, COPD, and ILD and evaluated the degree of coincidence between actual and estimated data.

Statistical Analysis

The results are reported as mean ± standard deviation (SD). Differences between the groups were evaluated using Student's *t*-test. Correlations between variables were determined using Pearson's correlation coefficient. The correlation statistics were interpreted as slight (<0.2), fair (0.2–0.4), moderate (0.4–0.6), substantial (0.6–0.8), or almost perfect (>0.8) agreement.[17] Multivariate linear regression analysis was performed to identify parameters predictive of VC, FVC, and $FEV_{1.0}$ using age, sex, height, body weight, resistance of 5 Hz (R5), resistance of 20 Hz (R20), reactance of 5 Hz (X5), resonant frequency (Fres), and reactance area (ALX) as independent variables. The bias of the equations was expressed as the mean difference between the estimated data and the actual data (sum of [estimated data − actual data]/[N]). The root mean squared error (RMSE) was calculated as the square root of (sum of squared errors of the estimate/[N]). Agreement between the equations was evaluated with Bland-Altman plots using the 95% limits of agreement (LOA), which were calculated as the average difference ± 1.96 SDs. The 95% confidence intervals were computed for all variables. All tests were two-tailed, and a *P*-value of <0.05 was considered to be statistically significant. A kappa value of >0.6 was interpreted to be within a permissive range. All statistical analyses were performed using SPSS version 22 for Windows (IBM, Tokyo, Japan).

Results

Clinical Characteristics of Patients in the Study

Among the 3581 subjects identified, 3113 underwent spirometry simultaneously with FOT. The subjects who did not meet inclusion criteria (n = 2015) and those with suboptimal spirometry data (n = 415) were excluded; finally, data from 683 subjects (378 men, 305 women) were included in the final analysis (Figure 1). Among them, 388 subjects had asthma, 128 subjects had COPD, and 167 subjects had ILD.

The characteristics of each patients group are presented in Table 1. Patients of the asthma group were younger than those of the other groups, and spirometry data of most patients were within the normal limits. $FEV_{1.0}$/FVC and %$FEV_{1.0}$ were significantly lower in the COPD group than in the other groups. %VC was significantly lower in the ILD group than in the other groups. With regard to FOT data, R20

Table 1 Characteristics of Study Subjects

Parameters	Asthma	COPD	ILD
Subjects	388	128	167
Sex, male/female	151/237	121/7	106/61
Age, years	54 ± 17	72 ± 9	69 ± 9
Height (cm)	159.9 ± 8.5	163.6 ± 6.6	159.4 ± 9.2
Body weight (kg)	60.6 ± 11.9	59.3 ± 11.0	58.8 ± 11.6
Smoking (never/current/ past/unknown)	215/37/74/62	0/32/96/0	58/12/89/8
Pulmonary function tests			
VC (l)	3.08 ± 0.83	3.02 ± 0.90	2.54 ± 0.84[†#]
%VC (%)	103.5 ± 18.2	93.3 ± 24.2*	87.0 ± 21.1[†#]
FVC (l)	3.05 ± 0.84	2.95 ± 0.92	2.53 ± 0.84[†#]
%FVC (%)	102.6 ± 19.3	91.2 ± 25.1*	86.7 ± 21.2[†]
$FEV_{1.0}$ (l)	2.29 ± 0.76	1.62 ± 0.65*	2.06 ± 0.63[†#]
%$FEV_{1.0}$ (%)	92.1 ± 20.4	69.4 ± 23.9*	98.8 ± 21.5[†#]
$FEV_{1.0}$/FVC	0.74 ± 0.11	0.54 ± 0.11*	0.83 ± 0.08[†#]
MostGraph-01 data			
R5	3.78 ± 1.60	3.58 ± 1.70	3.59 ± 1.51
R20	3.03 ± 1.17	2.74 ± 1.14*	2.80 ± 1.16[†]
X5	−0.94 ± 1.28	−1.54 ± 1.72*	−0.90 ± 0.66[#]
Fres	9.54 ± 4.38	12.63 ± 6.10*	10.00 ± 3.22[#]
ALX	5.73 ± 10.60	11.39 ± 16.21*	4.55 ± 4.41[#]

Notes: Results are reported as the mean ± standard deviation. *P < 0.05: vs asthma [†]P < 0.05: vs asthma, [#]P < 0.05: vs COPD.
Abbreviations: ALX, reactance area; COPD, chronic obstructive pulmonary disease; $FEV_{1.0}$, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; ILD, interstitial lung disease; R5, resistance at 5 Hz; R20, resistance at 20 Hz; VC, vital capacity; X5, reactance at 5 Hz.

values were significantly higher in the asthma group than in the other groups. X5 values were significantly lower and Fres and ALX values were significantly higher in the COPD group than in the other groups.

Correlations Between Spirometry and FOT Data

Statistically significant correlations were observed between most spirometric and FOT parameters in all the groups (Table 2). R5 and R20 showed slight to moderate correlations with all spirometric data in all the groups. X5, Fres, and ALX demonstrated moderate or substantial correlations with VC, %VC, FVC, %FVC, $FEV_{1.0}$, and %$FEV_{1.0}$ in all the groups. $FEV_{1.0}$/FVC showed a relatively lower degree of correlation with all the FOT parameters than did the other spirometric parameters.

Calculation of Estimated VC, FVC, and $FEV_{1.0}$

We identified the parameters predictive of VC, FVC, or $FEV_{1.0}$, using age, sex, height, and body weight, along with

FOT parameters, as independent variables. The results of multivariate linear regression analysis are shown in Table 3–5. On the basis of these results, we generated regression equations for VC, FVC, and $FEV_{1.0}$ in each patient with asthma, COPD, and ILD (Table 6).

Correlations Between Actual and Estimated VC, FVC, and $FEV_{1.0}$

We observed statistically significant correlations between the actual and estimated VC, FVC, and $FEV_{1.0}$ (all $P < 0.001$; Figure 2, Table 7). The estimated VC, FVC, and $FEV_{1.0}$ demonstrated an almost perfect correlation with the actual VC, FVC, and $FEV_{1.0}$ in all the groups. In addition, differences between actual and estimated VC, FVC, and $FEV_{1.0}$ were relatively small in all the groups. However, the estimated data in the present study are still not identical to the actual data. The Bland-Altman plots are shown in Figure 3. The 95% LOA values are shown in Table 7.

Diagnostic Accuracy of Estimated Data for an $FEV_{1.0}$/FVC Ratio of <0.7 and Classification of COPD Grade

We evaluated the diagnostic accuracy of an $FEV_{1.0}$/FVC ratio of <0.7 and percentage error for the classification of

severity of COPD. As shown in Table 8, kappa value for an $FEV_{1.0}$/FVC ratio of <0.7 was within a permissible range. However, the sensitivity of an $FEV_{1.0}$/FVC ratio of <0.7 was relatively low. In addition, the diagnostic accuracy and kappa value for the classification of COPD grade were low.

Discussion

In the present study, separate regression equations for patients with asthma, COPD, and ILD were newly generated and the degree of coincidence between the actual and estimated data was evaluated. The estimated data showed significant correlations with the actual data in all the groups, and the mean differences between the actual and estimated data were relatively small in all the groups. However, the estimated data in the present study are still not identical to the actual data.

The present study demonstrated that most of the FOT indices were significantly correlated with spirometric indices in the asthma, COPD, and ILD groups. Previous studies have reported significant correlations between R5 and $FEV_{1.0}$ and between Xrs and $FEV_{1.0}$ in patients with asthma and COPD.[18,19] Correlations between R20 and $FEV_{1.0}$ in patients with asthma were also reported.[18] In addition, X5, Fres, and ALX are reportedly correlated with %FVC and $%FEV_{1.0}$ in

Table 2 Correlations Between Spirometric and MostGraph-01 Data

Parameter	VC	%VC	FVC	%FVC	$FEV_{1.0}$	$%FEV_{1.0}$	$FEV_{1.0}$/FVC
Asthma							
R5	−0.530*	−0.404*	−0.525*	−0.394*	−0.502*	−0.344*	−0.200*
R20	−0.486*	−0.314*	−0.474*	−0.298*	−0.436*	−0.264*	−0.138**
X5	0.507*	0.571*	0.518*	0.573*	0.546*	0.530*	0.369*
Fres	−0.536*	−0.652*	−0.558*	−0.666*	−0.616*	−0.633*	−0.499*
ALX	−0.462*	−0.519*	−0.472*	−0.521*	−0.503*	−0.490*	−0.363*
COPD							
R5	−0.417*	−0.390*	−0.427*	−0.398*	−0.504*	−0.451*	−0.377*
R20	−0.386*	−0.363*	−0.388*	−0.363*	−0.461*	−0.424*	−0.347*
X5	0.587*	0.591*	0.603*	0.603*	0.698*	0.671*	0.531*
Fres	−0.709*	−0.717*	−0.726*	−0.730*	−0.797*	−0.753*	−0.527*
ALX	−0.519*	−0.520*	−0.539*	−0.539*	−0.648*	−0.634*	−0.538*
ILD							
R5	−0.447*	−0.230**	−0.452*	−0.239**	−0.490*	−0.207**	0.005
R20	−0.415*	−0.157**	−0.422*	−0.170**	−0.467*	−0.172**	−0.027
X5	0.661*	0.734*	0.661*	0.732*	0.623*	0.542*	−0.335*
Fres	−0.663*	−0.788*	−0.659*	−0.780*	−0.614*	−0.560*	0.356*
ALX	−0.634*	0.707*	−0.635*	−0.706*	−0.607*	−0.548*	0.306*

Note: *P < 0.001, **P < 0.05.
Abbreviations: ALX, reactance area; COPD, chronic obstructive pulmonary disease; $FEV_{1.0}$, forced expiratory volume in 1 s; FVC, forced vital capacity; Fres, resonant frequency; ILD, interstitial lung disease; R5, resistance at 5 Hz; R20, resistance at 20 Hz; VC, vital capacity; X5, reactance at 5 Hz.

Table 3 Regression Coefficients for Parameters Predictive of Vital Capacity

Parameters	Unstandardized Coefficients		95% CI		
	B	SE	Low	High	*P*-value
Asthma					
Age	−0.016	0.001	−0.018	−0.013	<0.001
Sex	0.519	0.058	0.405	0.632	<0.001
Height	0.026	0.004	0.019	0.034	<0.001
Body weight	0.006	0.002	0.002	0.009	<0.05
R5	0.191	0.052	0.088	0.294	<0.001
R20	−0.330	0.066	−0.459	−0.201	<0.001
X5	0.263	0.102	0.062	0.463	<0.05
Fres	−0.102	0.012	−0.126	−0.077	<0.001
ALX	0.042	0.010	0.022	0.063	<0.001
COPD					
Age	−0.021	0.005	−0.031	−0.011	<0.001
Sex	0.741	0.189	0.366	1.115	<0.001
Height	0.025	0.008	0.009	0.042	<0.05
Body weight	0.007	0.004	−0.002	0.015	0.146
R5	0.307	0.111	0.088	0.526	<0.05
R20	−0.476	0.150	−0.772	−0.180	<0.05
X5	0.365	0.152	0.064	0.665	<0.05
Fres	−0.121	0.018	−0.157	−0.084	<0.001
ALX	0.053	0.014	0.025	0.082	<0.001
ILD					
Age	−0.004	0.003	−0.011	0.003	0.303
Sex	0.446	0.094	0.259	0.632	<0.001
Height	0.022	0.006	0.011	0.033	<0.001
Body weight	0.012	0.003	0.006	0.018	<0.001
R5	0.263	0.097	0.072	0.455	<0.05
R20	−0.393	0.126	−0.642	−0.143	<0.05
X5	0.310	0.219	−0.123	0.744	0.159
Fres	−0.197	0.028	−0.252	−0.142	<0.001
ALX	0.080	0.032	0.017	0.142	<0.05

Abbreviations: ALX, reactance area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Fres, resonant frequency; ILD, interstitial lung disease; R5, resistance at 5 Hz; R20, resistance at 20 Hz; SE, standard error; X5, reactance at 5 Hz.

Table 4 Regression Coefficients for Parameters Predictive of Forced Vital Capacity

Parameters	Unstandardized Coefficients		95% CI		
	β	SE	Low	High	*P*-value
Asthma					
Age	−0.017	0.001	−0.019	−0.014	<0.001
Sex	0.469	0.061	0.350	0.588	<0.001
Height	0.027	0.004	0.020	0.035	<0.001
Body weight	0.005	0.002	0.001	0.009	<0.05
R5	0.199	0.055	0.091	0.307	<0.001
R20	−0.340	0.069	−0.475	−0.205	<0.001
X5	0.227	0.107	0.018	0.437	<0.05
Fres	−0.113	0.013	−0.138	−0.087	<0.001
ALX	0.041	0.011	0.020	0.062	<0.001
COPD					
Age	−0.021	0.005	−0.032	−0.011	<0.001
Sex	0.708	0.201	0.310	1.107	<0.05
Height	0.022	0.009	0.005	0.039	<0.05
Body weight	0.005	0.005	−0.004	0.015	0.268
R5	0.290	0.118	0.057	0.523	<0.05
R20	−0.450	0.159	−0.765	−0.135	<0.05
X5	0.314	0.161	−0.006	0.633	0.054
Fres	−0.129	0.020	−0.167	−0.090	<0.001
ALX	0.048	0.015	0.018	0.079	<0.05
ILD					
Age	−0.004	0.004	−0.011	0.004	0.334
Sex	0.440	0.098	0.247	0.633	<0.001
Height	0.022	0.006	0.011	0.034	<0.001
Body weight	0.011	0.003	0.004	0.017	<0.05
R5	0.294	0.100	0.096	0.493	<0.05
R20	−0.436	0.131	−0.695	−0.178	<0.05
X5	0.323	0.227	−0.125	0.772	0.157
Fres	−0.194	0.029	−0.251	−0.136	<0.001
ALX	0.077	0.033	0.013	0.142	<0.05

Abbreviations: ALX, reactance area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Fres, resonant frequency; ILD, interstitial lung disease; R5, resistance at 5 Hz; R20, resistance at 20 Hz; SE, standard error; X5, reactance at 5 Hz.

patients with ILD.[13] Similar to the results of these previous reports, the results of our study showed significant correlations between most FOT indices and spirometric indices in patients with asthma, COPD, and ILD.

In our previous report, the estimated data in the validation study did not show high accuracy.[9] The previous study had included healthy subjects and patients with various respiratory diseases, which is possibly the reason behind this low accuracy. FOT measures the impedance of the respiratory system, which includes the resistance and reactance of the respiratory system. Rrs reflects the dissipative mechanical property of the lung (viscous resistance). Rrs increases with an increase in airway obstruction, implying that Rrs is supposed to be

a measure of airway caliber.[20] Xrs is supposed to reflect the elastic and inertial properties of the lung. Previous reports showed that Fres may be a measure of both large and small airway function in COPD and a measure of increased lung elastic recoil resulting from fibrosis in ILD.[13] In addition, it was reported that X5 is a numerically negative value that is thought to be inversely related to the lung compliance.[21] FOT can sensitively detect increased airway resistance. Therefore, FOT has been used primarily for patients with obstructive lung diseases such as asthma and COPD.[1,3,4,11,12] On the contrary, Sugiyama et al reported that breath change in X5 may be a distinguishable characteristic of ILD rather than that in asthma or COPD.[22] It was also reported that Fres and ALX

Table 5 Regression Coefficients for Parameters Predictive of Forced Expiratory Volume in 1 s

Parameters	Unstandardized Coefficients		95% CI		
	β	SE	Low	High	P-value
Asthma					
Age	−0.022	0.001	−0.024	−0.020	<0.001
Sex	0.254	0.054	0.149	0.360	<0.001
Height	0.015	0.003	0.008	0.022	<0.001
Body weight	0.004	0.002	0.001	0.008	<0.05
R5	0.214	0.049	0.118	0.310	<0.001
R20	−0.375	0.061	−0.495	−0.255	<0.001
X5	0.080	0.095	−0.106	0.267	0.398
Fres	−0.122	0.011	−0.145	−0.099	<0.001
ALX	0.028	0.010	0.010	0.047	<0.05
COPD					
Age	−0.008	0.003	−0.015	−0.001	<0.05
Sex	0.161	0.128	−0.092	0.414	0.211
Height	0.005	0.005	−0.006	0.015	0.414
Body weight	0.015	0.003	0.009	0.021	<0.001
R5	0.199	0.075	0.051	0.347	<0.05
R20	−0.325	0.101	−0.525	−0.125	<0.05
X5	0.251	0.102	0.049	0.454	<0.05
Fres	−0.085	0.012	−0.109	−0.060	<0.001
ALX	0.030	0.010	0.011	0.049	<0.05
ILD					
Age	−0.006	0.003	−0.012	0	<0.05
Sex	0.301	0.077	0.148	0.453	<0.001
Height	0.020	0.005	0.011	0.029	<0.001
Body weight	0.006	0.003	0.001	0.011	<0.05
R5	0.221	0.079	0.064	0.377	<0.05
R20	−0.352	0.103	−0.556	−0.148	<0.05
X5	0.057	0.180	−0.298	0.412	0.753
Fres	−0.131	0.023	−0.176	−0.085	<0.001
ALX	0.030	0.026	−0.021	0.081	0.253

Abbreviations: ALX, reactance area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Fres, resonant frequency; ILD, interstitial lung disease; R5, resistance at 5 Hz; R20, resistance at 20 Hz; SE, standard error; X5, reactance at 5 Hz.

Table 6 Regression Equations for VC, FVC, and $FEV_{1.0}$ Corresponding to Patient with Asthma, COPD and ILD

Estimate Parameter	Regression Equation
Asthma	
VC	$-0.126 - age \times 0.016 + sex \times 0.519 + height \times 0.026 + weight \times 0.006 + R5 \times 0.191 - R20 \times 0.330 + X5 \times 0.263 - Fres \times 0.102 + ALX \times 0.042$
FVC	$0.048 - age \times 0.017 + sex \times 0.469 + height \times 0.027 + weight \times 0.005 + R5 \times 0.199 - R20 \times 0.340 + X5 \times 0.227 - Fres \times 0.113 + ALX \times 0.041$
$FEV_{1.0}$	$1.889 - age \times 0.022 + sex \times 0.254 + height \times 0.015 + weight \times 0.004 + R5 \times 0.214 - R20 \times 0.375 + X5 \times 0.080 - Fres \times 0.122 + ALX \times 0.028$
COPD	
VC	$0.212 - age \times 0.021 + sex \times 0.741 + height \times 0.025 + weight \times 0.007 + R5 \times 0.307 - R20 \times 0.476 + X5 \times 0.365 - Fres \times 0.121 + ALX \times 0.053$
FVC	$0.976 - age \times 0.021 + sex \times 0.708 + height \times 0.022 + weight \times 0.005 + R5 \times 0.290 - R20 \times 0.450 + X5 \times 0.314 - Fres \times 0.129 + ALX \times 0.048$
$FEV_{1.0}$	$1.538 - age \times 0.008 + sex \times 0.161 + height \times 0.005 + weight \times 0.015 + R5 \times 0.199 - R20 \times 0.325 + X5 \times 0.251 - Fres \times 0.085 + ALX \times 0.030$
ILD	
VC	$-0.124 - age \times 0.004 + sex \times 0.446 + height \times 0.022 + weight \times 0.012 + R5 \times 0.263 - R20 \times 0.393 + X5 \times 0.310 - Fres \times 0.197 + ALX \times 0.080$
FVC	$-0.088 - age \times 0.004 + sex \times 0.440 + height \times 0.022 + weight \times 0.011 + R5 \times 0.294 - R20 \times 0.436 + X5 \times 0.323 - Fres \times 0.194 + ALX \times 0.077$
$FEV_{1.0}$	$-0.141 - age \times 0.006 + sex \times 0.301 + height \times 0.020 + weight \times 0.006 + R5 \times 0.221 - R20 \times 0.352 + X5 \times 0.057 - Fres \times 0.131 + ALX \times 0.030$

Abbreviations: ALX, reactance area; COPD, chronic obstructive pulmonary disease; $FEV_{1.0}$, forced expiratory volume in 1 s; FVC, forced vital capacity; Fres, resonant frequency; ILD, interstitial lung disease; R5, resistance at 5 Hz; R20, resistance at 20 Hz; VC, vital capacity; X5, reactance at 5 Hz.

were significantly higher in patients with COPD than in those with asthma.[22] R5 and R20 were significantly lower in patients with ILD than in those with asthma, and Fres and ALX were significantly lower in patients with ILD than in those with COPD. The present study also showed significant differences in several FOT parameters between the asthma, COPD, and ILD groups (Table 1). Hence, we think that FOT data may indicate several features associated with each disease, and the data estimated using the generated regression equations may be more accurate in each disease.

We separately generated regression equations for asthma, COPD, and ILD and evaluated the degree of coincidence between the actual and estimated data. The VC, FVC, and

$FEV_{1.0}$ values estimated in this study showed a higher correlation with the actual values than those estimated using equation 2 in our previous study. The VC, FVC, and $FEV_{1.0}$ values estimated in the present study had a lower RMSE than did those obtained using equation 2 in our previous study, except for estimated FVC in patients with COPD. However, the estimated data in the present study are still not identical to the actual data. In addition, the sensitivity of an $FEV_{1.0}/FVC$ ratio of <0.7 and the diagnostic accuracy for the classification of the COPD grade using estimated data were low. Further studies are needed to generate more accurate regression equations for spirometric indices based on FOT measurements.
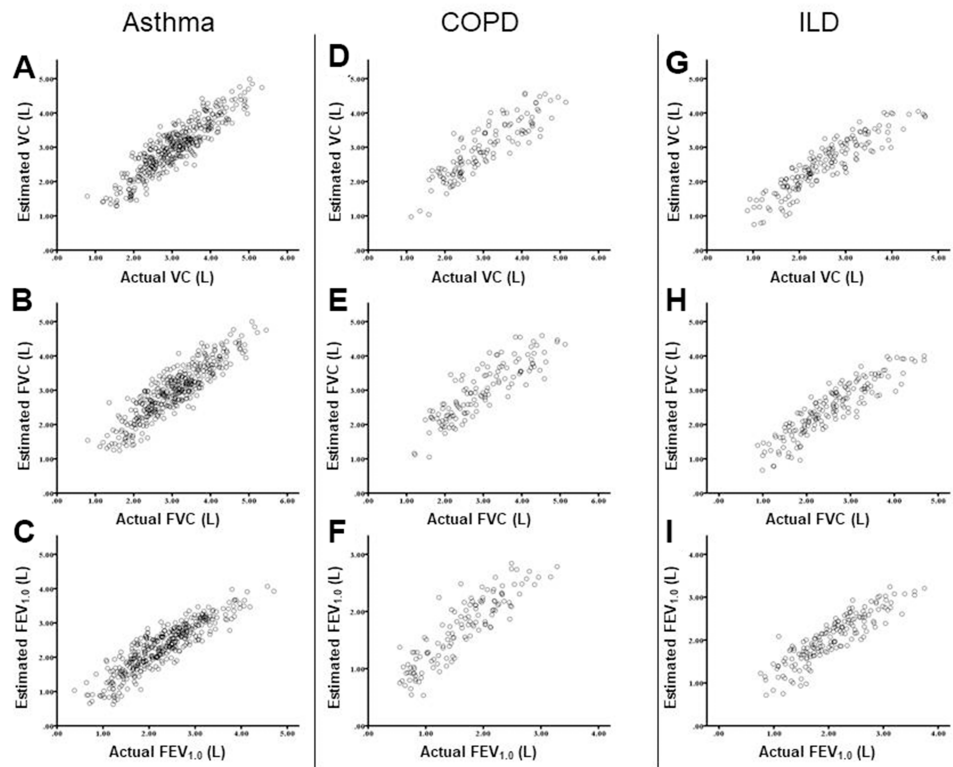
Figure 2 Correlations between actual and estimated VC, FVC, and $FEV_{1.0}$ in patients with asthma (**A–C**), COPD (**D–F**) and ILD (**G–I**).
Abbreviations: COPD, chronic obstructive pulmonary disease; $FEV_{1.0}$, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; VC, vital capacity.

Spirometry is the most commonly used pulmonary function test. Diagnosis of COPD requires spirometry. Spirometry can be used to evaluate other obstructive pulmonary diseases, including asthma, and restrictive pulmonary diseases, such as ILD. However, the forceful expiratory and inspiratory maneuvers in spirometry require good patient cooperation. Elderly patients and patients with cognitive impairment sometimes face difficulties in undergoing spirometry. Actually, studies concerning the quality of spirometry showed that only 33.4% of the elderly patients were able to undergo

Table 7 Correlation Between Actual and Estimated Data and Performance of Estimation Equations

	r (95% CI)	*P*-value	Bias (95% CI)	+1.96SD	−1.96SD	RMSE
Asthma						
VC	0.900 (0.879–0.917)	<0.001	−0.073 (−0.108–−0.037)	0.647	−0.792	0.367
FVC	0.895 (0.873–0.913)	<0.001	−0.069 (−0.107–−0.032)	0.683	−0.821	0.382
$FEV_{1.0}$	0.898 (0.877–0.916)	<0.001	0.017 (−0.017–0.050)	0.686	−0.653	0.335
COPD						
VC	0.876 (0.828–0.911)	<0.001	−0.064 (−0.140–0.012)	0.806	−0.933	0.438
FVC	0.866 (0.815–0.904)	<0.001	0.027 (−0.054–0.108)	0.952	−0.897	0.461
$FEV_{1.0}$	0.893 (0.851–0.923)	<0.001	0.069 (0.017–0.120)	0.656	−0.518	0.300
ILD						
VC	0.909 (0.878–0.932)	<0.001	−0.040 (−0.935–−0.129)	0.656	−0.737	0.350
FVC	0.903 (0.871–0.923)	<0.001	−0.071 (−0.126–−0.015)	0.651	−0.792	0.366
$FEV_{1.0}$	0.891 (0.855–0.919)	<0.001	−0.002 (−0.045–0.042)	0.569	−0.572	0.285

Note: Bias (estimated data − actual data) is expressed as the mean and 95% CI.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; $FEV_{1.0}$, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; RMSE, root mean squared error; SD, standard deviation; VC, vital capacity.
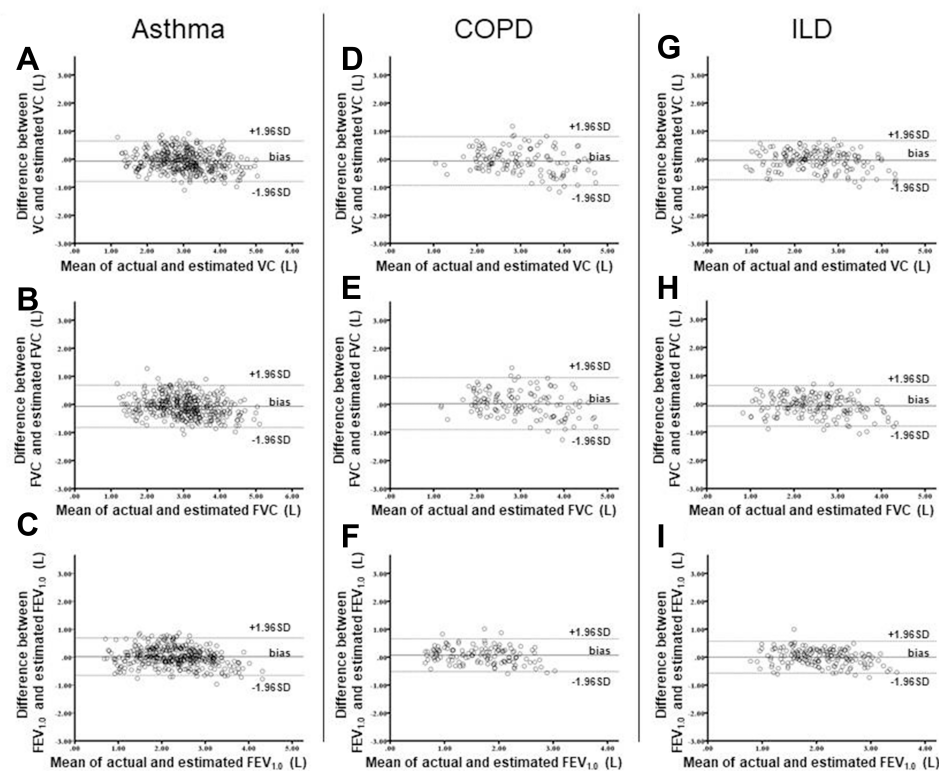
Figure 3 Bland-Altman plots comparing actual and estimated VC, FVC, and $FEV_{1.0}$ in patients with asthma (**A–C**), COPD (**D–F**) and ILD (**G–I**). The bias of the equations is expressed as the mean difference between the estimated data and the actual data (sum of [estimated data − actual data]/[N]).
Abbreviations: COPD, chronic obstructive pulmonary disease; $FEV_{1.0}$, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; SD, standard deviation; VC, vital capacity.

spirometry such that all the quality criteria defined by ATS/ERS guidelines are fulfilled[23] and that this proportion was even lower in the advanced elderly patients.[24–26] Our methods may have a potential clinical usability for evaluating lung function indices in such patients.

There are several limitations to this study. First, the present study was retrospective in nature. Second, the number of patients in each group was small. Third, no children were evaluated. Fourth, we used the MostGraph-01 to measure respiratory impedance, but not the MasterScreen IOS-J (CareFusion, San Diego, CA, USA). A previous report

showed that these devices do not necessarily generate identical impedance values.[27] Fifth, this study included only Japanese subjects. Sixth, our analysis used the oscillatory index in the whole-breath phase, but not the inspiratory or expiratory phases. Reportedly, breath-dependent changes in FOT data may be useful in assessing respiratory diseases.[12,22] Seventh, the number of excluded subjects based on non-acceptability of spirometric data was relatively high (38% of population). The present study had included data on many patients who came to the participating institutions at first visit and had symptoms such as cough, sputum, and dyspnea. In such patients, it was

Table 8 Diagnostic Accuracy of $FEV_{1.0}$/FVC<0.7, and Percentage Error in the Classification of Severity of COPD

	Sensitivity	Specificity	Diagnostic Accuracy	Kappa value
$FEV_{1.0}$/FVC < 0.7	170/243 (70%)	419/440 (95%)	599/683 (88%)	0.685

COPD grade
  Grade I (80% < %$FEV_{1.0}$)
  Grade II (50% < %$FEV_{1.0}$ ≦ 80%)
  Grade III (30% < %$FEV_{1.0}$ ≦ 50%)
  Grade IV (%$FEV_{1.0}$ < 30%)
	
	18/28 (64%)
	45/62 (73%)
	19/29 (66%)
	1/9 (11%)
		
		89/100 (89%)
		47/66 (71%)
		86/99 (87%)
		117/119 (98%)
			
			107/128 (84%)
			92/128 (72%)
			105/128 (82%)
			118/128 (92%)
				0.459

Note: COPD grade was classified based on the Global Initiative for Obstructive Lung Disease criteria.
Abbreviations: COPD, chronic obstructive pulmonary disease; $FEV_{1.0}$, forced expiratory volume in 1 s; FVC, forced vital capacity.

difficult to perform adequate spirometry. In addition, some elderly patients were not able to perform adequate spirometry-related maneuvers because of asynesis. Eighth, we did not evaluate the validity of regression equations using a separate data set.

Conclusion

The VC, FVC, and $FEV_{1.0}$ values estimated in this study showed a higher correlation with the actual values than those estimated in our previous study. However, the estimated data in the present study did not completely correspond to the actual data. Further studies are needed to generate more accurate regression equations for spirometric indices based on FOT measurements.

Abbreviations

95% LOA, 95% limits of agreement; ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; $FEV_{1.0}$, forced expiratory volume in 1 s; FOT, forced oscillometry; FVC, forced vital capacity; ILD, interstitial lung disease; Rrs, resistance; SD, standard deviation; VC, vital capacity; Xrs, reactance.

Ethics Approval and Informed Consent

The study protocol was approved by the ethical committees of Ehime University Hospital (Institutional Review Board number; 1,907,004) and Sumitomo Besshi Hospital (Institutional Review Board number; 155). The need for patient consent was waived because this was a noninterventional and retrospective study. However, participants were allowed to opt out of the study. We confirm that patient confidentiality was maintained.

Disclosure

All authors declare no potential conflicts of interest with regard to this work.

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